Arent Fox
ATTORNEYS AT LAW

Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, NW
Washington, DC 20036-5339
202/857-6000
Fax 202/857-6395
www.arentfox.com

Peter S. Reichertz
202/857-6378
reicherp@arentfox.com

March 17, 2000

BY HAND
Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket 78N-036L
Comments CP7 and CP8; Petition for
Reconsideration of Denial of Citizen Petitions

Dear Sir/Madam:

The undersigned, on behalf of C.B. Fleet Company, Incorporated, submits this Petition for Reconsideration by the Commissioner of Food and Drugs with regard to the May 22, 1998, decisions in Docket 78N-036L, CP7 and CP8, denying the requested actions.

DECISION INVOLVED

On November 12, 1987, we filed on behalf of C.B. Fleet Company, Incorporated, the above-referenced Citizen Petitions.

CP7 requested amendment of the Tentative Final Monograph for OTC Laxative Drug Products to include bisacodyl in an enema dosage form. On October 26, 1989, the Agency through a letter from Dr. William Gilbertson, indicated that 10mg of bisacodyl administered in a 37.5mL aqueous suspension rectal enema formulation "can be generally recognized as safe and effective as a laxative for adults and children 12 years of age and over". (See Exhibit A).

CP8 requested approval of six additional bowel cleansing systems, all including bisacodyl. Also by letter dated October 26, 1989, the Agency indicated that two of the six kits would be recommended for inclusion in the Final Monograph as the "data were sufficient to support" their effectiveness. (See Exhibit B).

By letter dated May 22, 1998, the Agency denied these petitions due to safety concerns with bisacodyl. (See Exhibit C). It indicated that, because of these concerns, the Agency

did "not consider it appropriate, at this time, to grant your petition requests", but that it would "be happy to reconsider your petition requests should data become available to support the safety of bisacodyl". (Exhibit C, page 2).

STATEMENT OF GROUNDS

Please note that the Agency has concluded that bisacodyl is safe, and that "the data support the safety of bisacodyl as a Category I OTC laxative ingredient". (See letter dated February 10, 2000, Docket 78N-036L, Rpt. 14, Exhibit D).

As bisacodyl has now been found safe, C.B. Fleet Company, Incorporated, requests that the Agency reconsider the denial of the above-referenced citizen petitions, and reinstate the findings of the two October 26, 1989, letters referenced above, which would include bisacodyl in an enema dosage form and prep kits consisting of Sodium Phosphates Oral Solution/Oral Bisacodyl and either a bisacodyl suppository or a bisacodyl enema in the Final Monograph on OTC Laxative Drug Products for Human Use. C.B. Fleet Company, Incorporated, requests that the Agency include these findings in the Final Monograph on OTC Laxative Drug Products.

* * * *

Should there be any questions concerning this Petition, please contact the undersigned.

Respectfully submitted,

Peter S. Reichertz
Arent Fox Kintner Plotkin & Kahn, PLLC
1050 Connecticut Avenue, N.W.
Washington, D.C. 20036-5339
202/857-6378
202/857-6395 (fax)

As counsel to C.B. Fleet Company, Incorporated

In Triplicate (CP7)
(CP8)

OCT 26 1989

~~OCT 25 1989~~

Peter S. Reichertz, Esq.
Arent, Fox, Kintner, Plotkin & Kahn
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Re: Docket No. 78N-036L
Comments No. CP0007
and AMD0003

Dear Mr. Reichertz:

This letter concerns your citizen petition (coded CP0007) submitted on behalf of the C. B. Fleet Company, Inc., dated November 12, 1987 and filed with the Dockets Management Branch on November 13, 1987. The petition requested that the tentative final monograph on OTC laxative drug products be amended to include an enema dosage form for the ingredient bisacodyl and to provide for its use as a post-evacuant in conjunction with a barium enema.

In my letter of January 12, 1988, I informed you that we were in the process of evaluating your petition and that additional data were needed for us to complete our evaluation. On May 17, 1988 you provided the additional data requested in my letter. This submission was coded AMD0003 by the agency.

We have completed our review and determined that a 10-mg dose of bisacodyl (administered in a 37.5 milliliter (mL) aqueous suspension rectal enema formulation) is safe and effective for use by adults and children 12 years of age and over, but that safety in children under 12 years of age and effectiveness as a post-evacuant at any age have not been demonstrated.

We have the following specific comments regarding the studies that were submitted:

The study by Salen and Keating compared two dosages of a bisacodyl enema with a bisacodyl suppository and a bisacodyl microenema. One hundred and four patients (101 male, 3 female, ages 24-88) were entered in the study; 96 patients were evaluated. One enema unit or one suppository was given to each patient 1 to 3 hours prior to the examination. Evaluation criteria included the time to first response, the number of bowel movements, the presence or absence of abdominal or other discomfort, and the adequacy of preparation for proctoscopic examination.

Fifty-nine percent of the patients (13 out of 22) who received the bisacodyl enema responded within 15 minutes compared with a

32-percent response within 15 minutes for the patients (8 out of 25) who received the bisacodyl suppository and a 38 percent response for the patients (9 out of 24) who received the bisacodyl microenema. Seventy-three percent of the bisacodyl enema patients (16 out of 22) were rated as having adequate bowel preparation for proctoscopic examination compared with ratings of 72 percent (18 out of 25 patients) and 71 percent (17 out of 24 patients), respectively, for the bisacodyl suppository and the bisacodyl microenema.

Based on the above, the agency has determined that only the criterion "time to response" provides information suggesting that the bisacodyl products can be differentiated from one another. Because a vehicle control was not used, this complicates interpretation of the results. Further, the bisacodyl enema formulation tested is somewhat different from the marketed formulation. The sponsor concludes that the glycerin and methylcellulose in the enema formulations do not individually contribute to the laxative effect of the product. While the quantities of each ingredient probably do little, we do not know their effect in combination.

The question to be addressed by the study is not the laxative activity of bisacodyl, but whether an enema formulation is as effective as a suppository formulation of this ingredient in producing laxation. Based on the 59-percent patient response rate within 15 minutes for the bisacodyl enema and the 32-percent patient response rate for the bisacodyl suppository control group, we find that the study, although qualitative and not optimally designed, provides substantial evidence that the enema containing 10 milligrams (mg) bisacodyl in a 37.5 mL aqueous suspension is at least as effective as, and can be substituted for, the 10-mg bisacodyl suppository.

The study by Swerdlow consisted of administration of one unit of bisacodyl enema (containing 10 mg in 37.5 mL) to each of 20 hospitalized or office subjects from 1 to 3 hours prior to proctoscopic examination. The same evaluation criteria as in the Salen and Keating study were used. The study showed a 90-percent response rate with a mean time of 10 minutes to first response after the administration of the bisacodyl enema. The bowel preparation was rated as adequate for 95-percent (19 out of 20) of the patients. Cramping was reported in 10 percent of the patients (2 out of 20). Although this study was uncontrolled, its favorable results are of value primarily as support for the results of the Salen and Keating study.

The study by Kaye and Solomon is a report on the use of bisacodyl in propylene glycol as an additive to barium enema suspensions. Twenty mg of bisacodyl was used in 109 cases and 10 mg was used in an additional 39 cases. Although the authors report bisacodyl in propylene glycol enema useful as an addition to the barium suspension, the study is uncontrolled and involves a bisacodyl formulation and dose different from that proposed in your petition. Therefore, this study does not provide substantial evidence to support the use of the proposed bisacodyl enema formulation as a post-evacuant in conjunction with a barium enema.

The study by Hagilner and Ostrum was a randomized, double-blind trial in 200 patients scheduled to undergo barium enema procedures in which the effectiveness of bisacodyl enema was compared with Clysodrast^{R} enema (3 mg of bisacodyl and 5 gm of tannic acid in 1400 mL of water) as a post-evacuant for barium enemas. The evaluation of drug efficacy was based on the post-evacuant film for:

a) Final diagnosis after barium enema,

b) Overall impression of the test material as a post-evacuant (excellent, good, fair, or poor),

c) Overall impression of the test material's ability to improve the mucosal pattern (excellent, good, fair, or poor).

While there was little difference between bisacodyl (72 percent of tests rated excellent) versus Clysodrast^{R} (70 percent of tests rated excellent) as post-evacuants, bisacodyl scored poorly on its ability to improve the mucosal pattern. Only 7 percent of the bisacodyl patients (7 out of 100) were rated as excellent in improvement of the mucosal pattern following its use as a post-evacuant, while 79 percent of the patients (79 out of 100) were rated as showing fair or poor improvement. By comparison, 53 percent of the Clysodrast^{R} patients (53 out of 100) were rated as excellent in improvement of the mucosal pattern with only 27 percent (27 out of 100) rated as showing fair or poor improvement. There were no differences in patient complaints between the groups; 84 percent of the patients had no complaints.

On the basis of this study, we cannot conclude that bisacodyl enema is safe and effective as a post-evacuant for barium enema. It does not appear to be as effective for improving the mucosal pattern as the approved Clysodrast^{R}. The usefulness of a post-evacuant is not merely to get rid of barium after a procedure, but to add to the radiologist's ability to assess

colonic pathology. On the post-evacuant film, with or without air contrast, mucosal integrity may be better defined, so that diagnostic accuracy is enhanced. This is the case with Clysodrast[R], but not with the bisacodyl formulation used in this study. We, therefore, cannot conclude, on the basis of the data provided, that bisacodyl enema is effective as a post-evacuant for barium enema.

Based on the data provided, we are able to conclude that 10 mg of bisacodyl administered in a 37.5 mL aqueous suspension rectal enema formulation can be generally recognized as safe and effective as a laxative for adults and children 12 years of age and over. Effectiveness as a post-evacuant in conjunction with a barium enema has not been demonstrated on the basis of the information provided. The safety and effectiveness of the formulation as either a laxative or as a post-evacuant has also not been demonstrated for children under 12 years of age because no studies in children were submitted. Use of this bisacodyl enema formulation as part of a bowel cleansing system is addressed in my other letter to you of this date.

Based on the above, we plan to recommend to the Commissioner that proposed 21 CFR 334.60(c)(1)(ii) be changed to read "Rectal dosage forms" from the currently proposed "Rectal suppository dosage forms," and that the following be added to proposed 21 CFR 334.60(d)(2):

> Rectal enema dosage: Adults and children 12 years of age and over: 10 milligrams bisacodyl in 37.5 milliliters of aqueous suspension in a single daily dose. Children under 12 years of age: Consult a doctor.

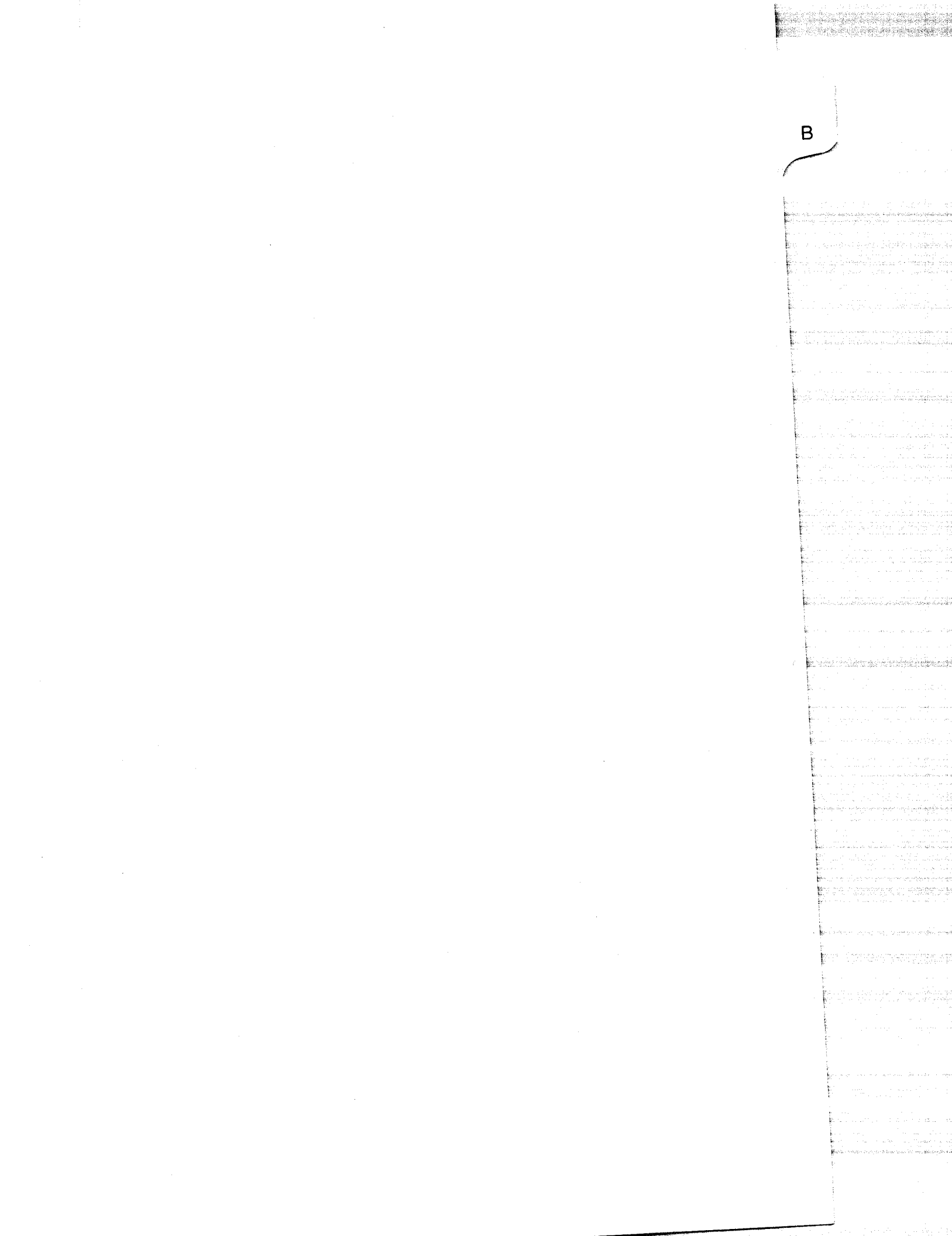
The Division of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your petition in the above manner in the final monograph for OTC laxative drug products, which will be published in a future issue of the FEDERAL REGISTER. Following that publication, you may file a citizen petition to amend the final monograph or file a new drug application for the post-evacuant claim for bisacodyl enema, as well as for its use as a laxative in children under 12 years of age.

Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket

number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fisher Lane, Rockville, MD 20857.

Sincerely yours,

William E. Gilbertson, Pharm. D.
Director
Division of OTC Drug Evaluation
Office of Drug Standards
Center for Drug Evaluation and Research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OCT 26 1989

Peter S. Reichertz, Esq.
Arent, Fox, Kintner, Plotkin & Kahn
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Re: Docket No. 78N-036L
Comments No. CP0008
and SUP005

Dear Mr. Reichertz:

This letter concerns your citizen petition (Coded CP0008) submitted on behalf of the C. B. Fleet Company, Inc., dated November 12, 1987, and filed under Docket No. 78N-036L in the Dockets Management Branch on November 13, 1987. The petition requested that the tentative final monograph for OTC laxative drug products (published in the FEDERAL REGISTER of January 15, 1985; 50 FR 2124) be amended to include 6 additional bowel cleansing systems.

In my letter of May 16, 1988, I informed you that we were in the process of evaluating your petition and that additional data were needed for us to complete our evaluation. On August 16, 1988 you provided the additional data requested in my letter. This submission was coded SUP005 by the agency.

We have completed our review and determined that two of the proposed bowel cleansing systems are safe and effective for use by adults and children 12 years of age and over. The other four proposed bowel cleansing systems require additional data to demonstrate their safety and effectiveness.

We have the following specific comments regarding each of the six bowel cleansing systems and the data submitted in support of them:

Kit Number 1: A kit containing the following 3 laxative drug products for sequential administration: 7.56 grams (g) of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 milligrams (mg) of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, 10 mg of bisacodyl administered by suppository at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

Kit number 1 substitutes 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate for 25 g of magnesium citrate in the bowel cleansing system listed in § 334.32(a) of the OTC laxative tentative final monograph (50 FR 2153). It also slightly alters the current dosing regimens of oral and rectal bisacodyl from 15-20 mg bisacodyl orally 2 hours after magnesium citrate to 20 mg bisacodyl at least 3 hours after sodium phosphate/sodium biphosphate, and from 10 mg bisacodyl suppository 9 hours after oral bisacodyl and at least 2 hours before the x-ray to at least 9 hours after the oral bisacodyl and at least 1 hour before the x-ray. The proposed bowel cleansing system containing these dosages and regimen has been marketed for over 15 years.

Both magnesium citrate and sodium phosphate/sodium biphosphate are listed in the OTC laxative tentative final monograph as single ingredient Category I saline laxatives, and the dosages in the bowel cleansing systems would be the maximum single daily dose permitted for each. In addition, in § 334.80 professional labeling claims have been proposed for both magnesium citrate and sodium phosphate/sodium biphosphate for use as part of a bowel cleansing regimen in preparing the patient for surgery, x-ray, and endoscopy (50 FR 2157). The data provided included a summary report of a clinical evaluation of kit no. 1 compared to Evac-Q-Kit, a bowel cleansing system listed in § 334.32(b) of the OTC laxative tentative final monograph (50 FR 2153) and consisting of magnesium citrate, phenolphthalein, and a carbon dioxide-releasing suppository.

In this single blind randomized study of 108 patients being prepared for barium enema, 57 patients received kit number 1 and 51 patients received Evac-Q-Kit. Thirty-one percent of the patients treated with kit number 1 showed moderate to extensive gas retention after treatment compared with 53 percent of the patients treated with Evac-Q-Kit. Seventy five percent of the patients treated with kit number 1 showed good to excellent mucosal detail on examination compared to 54 percent of the patients treated with Evac-Q-Kit. Overall evaluation (satisfactory/unsatisfactory) of the colon preparation showed no significant difference between the two bowel cleansing systems. There were no significant differences in side effects produced by the two kits.

Although this study does not provide a comparison between kit number 1 and the most similar bowel cleansing system (magnesium citrate followed by bisacodyl), it does compare another Category I bowel cleansing system (magnesium citrate, phenolphthalein, and carbon dioxide-releasing suppositories, (§ 334.32(b), 50 FR 2156) with one in which sodium

phosphate/sodium biphosphate is substituted for magnesium citrate. The results of this study, together with other data already considered by the agency in the laxative tentative final monograph (50 FR 2137), support the contention that sodium phosphate and sodium biphosphate can be interchanged for magnesium citrate safely and effectively in a Category I bowel cleansing system. This interchangeability would apply to either of the bowel cleansing systems specified in proposed § 334.32 in the OTC laxative tentative final monograph (50 FR 2153). The safety and effectiveness of the dose and dose regimen proposed for kit number 1 are supported by previous agency findings in the tentative final monograph and by the data provided. Appropriate additions to § 334.32 will be included in the final monograph.

Kit Number 3: A kit containing the following 3 laxative drug products for sequential administration: 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, 10 mg of bisacodyl administered by enema 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

This kit is identical to kit number 1 except for the substitution of a 10 mg bisacodyl enema for the 10 mg bisacodyl suppository. As discussed in my other letter to you of this date, we concur that the submitted data support the substitution of the 10 mg bisacodyl enema formulation for the Category I 10 mg bisacodyl suppository.

We therefore concur that a Category I bowel cleansing system substituting a 10 mg bisacodyl enema for a 10 mg bisacodyl suppository is acceptable. Appropriate additions to § 334.32 will be included in the final monograph.

Kit Number 2: A kit containing the following 3 laxative drug products for sequential administration: 7.56 g of sodium phosphate and 20.2 g of sodium biphosphate in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the sodium phosphate/sodium biphosphate oral solution, and administration of a large volume liquid castile soap enema at least 9 hours after administration of the oral bisacodyl and at least 2 hours before the scheduled x-ray or examination.

Bowel cleansing kit number 2 is the same as bowel cleansing kits 1 and 3 except for the substitution of a soap enema in place of the bisacodyl suppository or bisacodyl enema. As noted in your submission of August 16, 1988 (SUP005), no

clinical studies of the liquid castile soap enema have been performed, although some textbooks of the 1940s and 1950s do refer to soap water enemas. No data on soap water enemas have been submitted to the OTC drug review and such products are not discussed in the OTC laxative tentative final monograph (50 FR 2124). In view of the literature reports noted in your own submission that soap enemas have caused adverse reactions and are irritating, as well as the lack of clinical data on their safety and effectiveness, there is no adequate basis to recommend approval of kit number 2 or any bowel cleansing kit containing a soap enema. Should the company wish to pursue approval of kits containing a soap enema, well-controlled clinical trials comparing a bowel cleansing kit with a soap enema to that with a bisacodyl enema or suppository will be necessary.

Kit Number 4: A kit containing the following 3 laxative drug products for sequential administration: 60 milliliters (mL) of castor oil emulsion in oral solution, 20 mg bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, 10 mg of bisacodyl administered by suppository at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

Proposed bowel cleansing kit number 4 is the same as kit number 1 but substitutes castor oil for sodium phosphate and sodium biphosphate. Castor oil is in Category I in the OTC laxative tentative final monograph both as a stimulant laxative and for use alone in preparing the colon for endoscopic examination. There is no discussion in the laxative tentative final monograph regarding the use of castor oil with other laxatives as part of a bowel cleansing regimen. The proposed combination in kit number 4 would combine two stimulant laxatives rather than a saline laxative and a stimulant laxative. Such a substitution must be supported by adequate clinical data. The argument that because each ingredient proposed for kit number 4 is separately approved for bowel cleansing in the OTC laxative tentative final monograph, the combination must be safe and effective as a bowel cleansing system is not in keeping with the agency's guidelines on OTC combination drug products. The discussion of FDA's combination policy in comment 88 in the laxative tentative final monograph clearly states that "data are necessary to establish the safety and effectiveness of other specific combinations or to demonstrate that the specific ingredients in a pharmacological class are chemically and pharmacologically interchangeable." (See 50 FR 2146.)

The study by Strates and Hofmann (Pharmatherapeutica, 5:57-61, 1987) was a single-blind randomized study of 195 patients being prepared for barium enema, in which one group of patients received 2 ounces (oz) of castor oil followed by tap water enemas, while the other group received magnesium citrate, phenolphthalein, and a bisacodyl suppository. This study did not demonstrate any significant differences between the two bowel cleansing systems, although some significant differences were noted in patient preference for the magnesium citrate-containing kit. The authors of this study also noted that a previous study by Irwin et al. (Gastroenterology, 67: 47-50, 1974) found that a bowel preparation kit containing magnesium citrate, phenolphthalein, and a carbon dioxide-releasing suppository gave significantly superior results in preparing patients for barium enema than did 2 oz of castor oil followed by cleansing enemas. Neither of the aforementioned studies provide the support needed to establish the safety and effectiveness of a bowel cleansing kit containing castor oil followed by a cleansing tap water enema, nor do these data support the safety and effectiveness of a kit containing castor oil followed by oral bisacodyl and a soap water enema (kit number 5), or castor oil followed by oral and then rectal bisacodyl (kit number 6).

It is not possible to predict whether the castor oil-containing kits would produce results equivalent to, better than, or worse than the magnesium citrate bowel cleansing systems currently proposed as Category I in the laxative tentative final monograph. Such a kit would contain only stimulant laxatives, and the repetitive administration of such active agents may not be needed and may cause an increase in adverse reactions. Data from well-controlled clinical studies comparing castor oil to magnesium citrate would be necessary for further evaluation of these proposed kits, and for the castor oil kit containing soap enema, a separate evaluation, as noted above for proposed kit number 2, would be necessary.

Kit number 5: A kit containing the following 3 laxative drug products for sequential administration: 60 mL of castor oil emulsion in oral solution, 20 mg bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, and administration of a large volume liquid castile soap enema (2/3 fluid oz of liquid castile soap) at least 9 hours after the administration of the oral bisacodyl and at least 2 hours before the scheduled x-ray or examination.

The deficiencies discussed for proposed kits number 2 and number 4 above apply equally to this proposed bowel cleansing system.

Kit number 6: A kit containing the following 3 laxative drug products for sequential administration: 60 mL of castor oil emulsion in oral solution, 20 mg of bisacodyl administered orally at least 3 hours after administration of the castor oil emulsion in oral solution, 10 mg of bisacodyl administered by enema at least 9 hours after the administration of the oral bisacodyl and at least 1 hour before the scheduled x-ray or examination.

The deficiencies mentioned in the discussion of proposed kit number 4 above apply equally to this proposed kit.

The Division of OTC Drug Evaluation is therefore proposing that the following bowel cleansing systems (identified as kit numbers 1 and 3 above) be included as Category I for adults and children 12 years of age and over in the final monograph for OTC laxative drug products:

A kit containing the following 3 laxative drug products for sequential administration: sodium phosphate/sodium biphosphate marketed as an oral solution identified in § 334.16(d) and bisacodyl identified in § 334.18(b) in both an oral dosage form and a suppository dosage form. (Kit number 1)

A kit containing the following 3 laxative drug products for sequential administration: sodium phosphate/sodium biphosphate marketed as an oral solution identified in § 334.16(d) and bisacodyl identified in § 334.18(b) in both an oral and an enema dosage form. (Kit number 3)

Please note that the dosage schedules for these kits will be included in § 334.66(d) in the final monograph and an appropriate cross-reference will be included in the above kit descriptions when included in § 334.32 of the final monograph.

The submitted data are insufficient to support the inclusion of your other proposed bowel cleansing kits (identified as kit numbers 2, 4, 5, and 6 above) as Category I at this time. Therefore, we are not proposing that any of those bowel cleansing systems be included in the OTC laxative final monograph.

The Division of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to your comment in the above manner in the final monograph for OTC laxative drug products, which will be published in a future issue of the FEDERAL REGISTER. Following that publication, you may file a citizen petition to amend the final monograph or file a new drug application for any of the kits not included in the monograph. Should the company wish to perform the clinical studies needed for any of these other kits, the agency would be glad to review proposed protocols.

Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,

William E. Gilbertson, Pharm. D.
Director
Division of OTC Drug Evaluation
Office of Drug Standards
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 22 1998

Peter S. Reichertz, Esq.
Arent, Fox, Kintner, Plotkin & Kahn
1050 Connecticut Avenue, NW
Washington, DC 20036-5339

Re: Docket No. 78N-036L
Comments No. CP7 and CP8.

Dear Mr. Reichertz:

We refer to your citizen petitions dated November 12, 1987, submitted on behalf of C.B. Fleet Company, Inc., requesting amendment of the tentative final monograph (TFM) for over-the-counter (OTC) laxative drug products.

CP7 requests that the TFM be amended to include an enema dosage form for the ingredient bisacodyl and to provide for its use as a post-evacuant in conjunction with a barium enema.

CP8 requests that the TFM be amended to include 6 additional bowel cleansing systems. Each system incorporates use of bisacodyl.

For the following reasons, the agency considers action on the petitions completed.

On October 26, 1989, Dr. Gilbertson issued a letter to you (copy enclosed) indicating that 10 milligrams (mg) of bisacodyl administered in a 37.5 milliliter (mL) aqueous suspension rectal enema formulation can be generally recognized as safe and effective as a laxative for adults and children 12 years of age and over. However, data did not support the effectiveness of bisacodyl enema as a post-evacuant for barium enema.

A second letter issued to you by Dr. Gilbertson on October 26, 1989 (copy enclosed), indicated that data were sufficient to support the effectiveness of 2 of the 6 bowel cleansing kits (i.e., Kit #1 containing sodium phosphate and sodium biphosphate/oral bisacodyl/bisacodyl suppository and Kit #2 containing sodium phosphate and sodium biphosphate/oral bisacodyl/bisacodyl enema).

We note that both petitions concern the stimulant laxative ingredient, bisacodyl. Because of recent safety concerns regarding bisacodyl (see May 10, 1996 letter from Dr. Debra Bowen, Director, Division of OTC Drug Products, copy enclosed), the agency does not consider it appropriate, at this time, to grant your petition requests.

Accordingly, your petitions 78N-036L\CP7 & CP8 are denied.

We will be happy to reconsider your petition requests should data become available to support the safety of bisacodyl.

If you have any questions regarding the petitions, please refer to the docket and comment numbers above, and submit all inquiries, in triplicate, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, MD 20857.

Sincerely yours,

Ronald G. Chesemore
for Associate Commissioner
for Regulatory Affairs

Enclosures

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Tetman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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FEB 10 2000

Martin M. Kaplan, M.D., J.D.
Vice President,
Drug Regulatory Affairs
Boehringer Ingelheim
900 Ridgeburg Road
P.O. Box 368
Ridgefield, Connecticut 06877-0368

Re: Docket No. 78N-036L
Comment No. RPT 14

Dear Dr. Kaplan:

Reference is made to your submission dated October 21, 1999, identified as Comment No. RPT 14, under Docket No. 78N-036L in the Dockets Management Branch, entitled "A Six Month Oral Gavage Carcinogenicity Study of Bisacodyl in the Heterozygous p53 Transgenic Mouse (Study No. 98R027)." This study was submitted to support the safety of bisacodyl as a Category I (safe and effective) over-the-counter (OTC) laxative drug ingredient.

We have the following comments on the study:

In the first week of treatment, heterozygous p53 transgenic mice received bisacodyl by oral gavage at doses of 0, 800, 4000, and 8000 mg/kg/day. The high dose of 8000 mg/kg/day was given as two daily doses of 4000 mg/kg administered 4 hours apart. Based upon recommendations received from the FDA's Center for Drug Evaluation and Research Carcinogenicity Assessment Committee (CAC), the mid dose was changed from 4000 to 2000 mg/kg/day and the low dose was changed from 800 to 500 mg/kg/day at the beginning of the second week of treatment. A positive control group received p-cresidine at 400 mg/kg/day.

There were no treatment-related findings of hyperplasia, metaplasia, or tumors for heterozygous p53 transgenic mice that received bisacodyl.

For heterozygous p53 transgenic mice that received the positive control, p-cresidine, neoplastic findings were observed in the urinary bladder that included transitional cell papilloma and

carcinoma for 4 of 30 (13.3 percent) of the animals. Additional findings in the urinary bladder included transitional epithelial hyperplasia for 26 of 30 (86.7 percent) of the animals, squamous metaplasia for 11 of 30 (36.7 percent) of the animals, transepithelial apoptosis for 13 of 30 (43.3 percent) of the animals, and spindle cell hyperplasia for 4 of 30 (13.3 percent) of the animals. The combined incidence of transitional cell papilloma, carcinoma, and hyperplasia, as well as squamous metaplasia, was 86.7 percent (26 of 30) of the animals.

For all groups including the control, undifferentiated sarcomas were observed in association with transponder identification chips. Survival rates were unaffected by treatment with bisacodyl. Body weight gain for female mice that received bisacodyl at 8000 mg/kg/day was impaired by >10 percent; however, final body weight was 94.2 percent of the control. Body weight gain and final body weight for male mice that received p-cresidine were impaired by >10 percent. Food consumption over the treatment period was significantly reduced for male and female mice that received p-cresidine. Bisacodyl treatment produced no increases in the frequency of micronuclei/ polychromatic erythrocytes (PCE) in the peripheral blood. Bisacodyl at 8000 mg/kg/day produced centrilobular hepatocellular hypertrophy characterized by the presence of enlarged cells with abundant eosinophilic cytoplasm in female mice.

Based on our review of your submission and other information available for bisacodyl (refer to our letters dated April 8, 1998 and March 23, 1999, coded as LET175 and LET180, respectively, filed under Docket No. 78N-036L in the Dockets Management Branch), we conclude the following:

1. The results of the carcinogenicity study with bisacodyl in heterozygous p53 transgenic mice are acceptable.

2. Bisacodyl at oral doses up to 8000 mg/kg/day was not found to be tumorigenic in heterozygous p53 transgenic mice.

3. Based on currently available information, no further carcinogenicity testing of bisacodyl is recommended. The totality of the data available do not suggest a human carcinogenic risk from bisacodyl when used as recommended.

Therefore, the data support the safety of bisacodyl as a Category I OTC laxative ingredient. The Division of OTC Drug Products intends to recommend to the Commissioner that the Agency respond to your submission in the above manner in an amendment to the final monograph for OTC laxative drug products.

Any comment you wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, room 1061, 5630 Fishers Lane, Rockville, MD 20852.

We hope this information will be helpful.

Sincerely yours,

Charles Ganley, M.D.
Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research